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(54) **Title:** AN IMPROVED AND STABLE PHARMACEUTICAL COMPOSITION CONTAINING SUBSTITUTED BENZIMIDAZOLES AND A PROCESS FOR ITS PREPARATION

(57) **Abstract:** The present invention relates to improved pharmaceutical preparations containing substituted benzimidazoles,(i.e.omeprazole, lansoprazole, pantoprazole, and rabeprazole). The preparations comprise an inert core, constituted by starch and sugar, surrounded by active coating containing at least one substituted benzimidazole in the micronized form, which is mixed with pharmaceutically acceptable non-alkaline and inert excipients, followed by intermediate coating and an enteric coating, in order to guarantee the integrity of the product until it reaches the proximal part of the small intestine, where the formulation will be disaggregated to facilitate the absorption of the substituted benzimidazole compound.

An improved and stable Pharmaceutical Composition containing substituted Benzimidazoles and a process for its preparation

Introduction

The present invention relates to an improved stable pharmaceutical composition containing substituted benzimidazoles useful in the treatment of gastric and duodenal ulcers and a process for its preparation. The present invention particularly relates to an improved pharmaceutical composition in the form of hard gelatin capsules containing substituted benzimidazoles such as omeprazole, lansoprazole, pantoprazole and rabeprazole. The pharmaceutical composition of the present invention guarantees the integrity of the composition until it reaches the proximal part of the small intestine, where the composition will be disaggregated to facilitate the absorption of the substituted benzimidazole compound contained therein. This invention also involves a process of preparing the above mentioned pharmaceutical composition

The present invention provides a stable pharmaceutical composition containing substituted benzimidazoles such as omeprazole, lansoprazole, pantoprazole and rabeprazole, useful for treating gastro intestinal ulcers. The pharmaceutical composition of the present invention is in the form of hard gelatin capsules suitable for oral administration. The composition of the present invention would dissolve in the intestine to facilitate absorption in the neutral / alkali environment.

Prior art of the invention

Benzimidazolic compounds such as omeprazole (5-methoxy-2(((4-methoxy-3, 5-di met hyl -2-pyridinyl)-methyl-sulfinyl)1H-benz imidazole), lansoprazole (2-((3-methyl-4-(2,2,2-trifluoroetoxy)-2-piridyl)methyl(sulfinyl 1H-benzimidazole) (U.S. Pat No. 4,628,098), pantoprazole (U.S. Pat. No. 4,758,579)), and and rabeprazole, are anti-ulcerous substances known for decreasing gastric acid secretion (Olbe L., et al., Gastroenterol., 83:193-198 (1982); Saton H. et al., Jpn. J. Pharmacol. 40 (suppl.), 226 (1986); Saton H, et al., J.Pharmacol. Exp. Ther, 248 (2), 806-815 (1989), These compounds are used in the therapeutics of diseases related to gastric acidity in mammals

and especially in humans, including gastric and duodenal ulcers, reflux oesophagitis, gastritis and duodenitis.

It is also known that these substituted benzimidazoles possess a very low level of solubility in water. They solubilize easily in alkaline solutions. They degrade quickly in acidic and neutral media (Pilbrand and Cederberg, Scand. J. Gastroenterol, 20 (Suppl. 108), p. 113-120 (1985)) and they are stabilized in the presence of alkaline reacting compounds.

The maximum stability of omeprazole solution is reached at pH 11 [Drug. Dev. Ind. Pharm., 21(8), 965 (1995)]. Degradation occurs very quickly below a pH of 7.0. On the other hand, it is necessary that the formulations dissolve quickly in the intestine, where the benzimidazolic compounds should be absorbed, i.e. when the pH becomes higher than 6.8. There are various prior art showing benzimidazoles such as omeprazole, lansoprazole, pantoprazole and rabeprazole with the above activity.

US Pat No. 2540979 describes an enteric-coated oral dosage form of Omeprazole, where the enteric coating is combined with a second and or first coating of a water insoluble wax layer. This method of preparation may prove to be inadequate for omeprazole due to the water insoluble wax layer preventing the release and dissolution of the Omeprazole .

U.S. Pat. No. 4,786,505 proposes the mixture of a mass of cellulose derivatives and disaggregants, with an appropriate amount of omeprazole and alkaline agents or alkaline salts of the drug, in order to obtain, by extrusion, a core which is spheronized and coated with gastroresistant agents dissolved in alcoholic solutions also containing considerable percentages of acetone. However, the pellets obtained may be extremely irregular in shape and dimensions, and this can have repercussions on a relative dispersion of the average weight of the capsules and of the respective dosage.

U.S. Pat. No. 5,385,739 and FR-A-2 692 146 describe pharmaceutical gastric protected dosage forms containing omeprazole wherein the active substance is diluted with

mannitol and applied to an inert core, followed by an insulating layer and gastric protected coating. The process requires the use of organic solvent throughout the three stages, with its' continuous exposure to ethanol may in the long run impact the health of operating personnel.

U.S. Pat. No. 5,399,700 concerns with the stabilization of benzimidazolic derivative compounds as cyclodextrin inclusion complexes. As Cyclodextrins are quite expensive, the product may loose the cost advantage.

WO 98/50019 relates to oral dosage forms containing omeprazole or lansoprazole, inside hard gelatine capsules, which are subsequently coated with gastroresistant or enteric polymers. During the coating with the polymers, the integrity of the gelatine capsules may suffer due to the action of the solvents.

U.S. Pat. No. 5,026,560 relates to spherical pellets consisting of a core coated with a binding agent which is coated with a mixture of powders containing lansoprazole, HPMC of low viscosity and magnesium or calcium carbonates as alkaline agents. The manufacturing process used was "powder coating", for drug layering which may lead to wastage of drug and also may not yield uniform pellets.

The US Patent 6489346, titled Substituted benzimidazole dosage forms and method of using same, discloses solid pharmaceutical composition in a dosage form that is not enteric-coated, the dosage form includes a suspension tablet, a chewable tablet, an effervescent powder, or an effervescent tablet. Also provided is a method for treating an acid-related gastrointestinal disorder in a subject in need thereof by administering to the subject a solid pharmaceutical composition. Due to the absence of enteric coating, the stability of the drug may not be optimum.

The US Patent 6248355, describes a composition of omeprazole without the use of alkaline- reacting compounds and in which the active ingredient is granulated together and compressed together along with inert ingredients followed by a coating of

intermediate coat containing one or several inert water soluble layer or layers which rapidly disintegrate in aqueous medium and contains non-acid inert pharma excipients. This layer comprises at least one polymer conventionally used in application where a film is provided by coating with such materials as sugars, polyethyleneglycol, polyvinylalcohol, hydroxy propyl methyl cellulose, an intermediate coat, and an enteric coating containing entero- soluble gastro resistants made of latex suspension of polymers such as cellulose acetate phthalate, methacrylic acid, methacrylic esters, methacrylic acid copolymers.

This process involves multi-step processing such as preparation of core, intermediate layer and enteric coatings and may involve a number of controlling points like dry mixing of the drug with inert excipients, granulation of the mass, lubrication, compression, followed by a coating of intermediate layer and finally coating by an enteric layer, thereby making the process a multi-step process with each step subjected to the active ingredient analysis thereby not only making the process cumbersome but also increasing the cost of the product.

Objectives of the present invention.

The main objective of the present invention is, therefore , to provide an improved stable pharmaceutical composition containing substituted benzimidazoles useful in the treatment of gastric and duodenal ulcers .

Another objective of the present invention is to provide an improved stable pharmaceutical composition containing substituted benzimidazoles useful in the treatment of gastric and duodenal ulcers without the necessity of using an alkali agent or alkali salt of the substituted benzimidazole for the stability of the formulation.

Yet another objective of the present invention is to provide an improved stable pharmaceutical composition containing substituted benzimidazoles useful in the treatment of gastric and duodenal ulcers by using most commonly available inert and non -acid / non-alkaline and safe pharmaceutical excipients to create an appropriate

microenvironment for the active drug , namely the substituted benzimidazoles , since they are unstable in acidic / neutral environment and to release the active ingredient only in an alkaline environment .

Still another objective of the present invention is to provide an improved stable pharmaceutical composition useful in the treatment of gastric and duodenal ulcers which does not release the drug in the stomach (acidic environment) but releases the drug (substituted benzimidazoles) in the intestine (alkaline environment) .

Still another objective of the present invention is to provide an improved and stable pharmaceutical composition containing substituted benzimidazoles as hard gelatin capsules useful in the treatment of gastric and duodenal ulcers to facilitate to disaggregate quickly in the neutral to alkaline environment in the intestine with complete dissolution of the substituted benzimidazoles in the intestine.

Yet another objective of the invention is to provide a process for the preparation of an improved and stable pharmaceutical composition containing substituted benzimidazoles useful in the treatment of gastric and duodenal ulcers as described above useful for oral adminstration in capsule form.

The present invention has been developed based on our finding that when some of the most commonly available pharmaceutically inert, non-alkaline / non- acid pharmaceutical excipients such as dicalcium phosphate, dioctyl sodium sulpho succinate, talc, titaniumdioxide, starch, sodium lauryl sulphate, micro crystalline cellulose powder, magnesium stearate and the like are mixed judiciously along with benzimidazoles such as omeprazole, lansoprazole, pantoprazole and rabeprazole, their salts or their mixtures and processed resulting in a composition which is stable during its passage through the stomach and remains in a microenvironment that is not acidic or lower than pH 7.0, at the same time when the composition exits from the stomach and reaches the proximal part of the intestine, the drug dissolves rapidly.

The present invention provides a composition composed of an inert core coated with a layer which contains the active ingredient(s) devoid of any alkali reacting compounds, coated in turn with an intermediate coat, also devoid of any alkali reacting compounds and a final external gastro resistant or enteric coating. The composition of the present invention is also characterized in that it does not dissolve in an acid medium, but dissolves quickly at an alkaline pH and present good stability in terms of dosage and in gastroresistance and dissolution in the small intestine.

The pharmaceutical composition of the present invention comprises an inert core, constituted by starch and sugar, coated with a layer containing at least one substituted benzimidazole in the micronized form, which is mixed with pharmaceutically acceptable non-alkaline and inert pharmaceutical excipients, this layer in turn being coated with an intermediate coating and an enteric coating.

The present invention provides an improved stable pharmaceutical composition as a hard gelatin capsule dosage containing a substituted benzimidazole (omeprazole, lansoprazole, pantoprazole and rabeprazole), or its salts or its mixture thereof, constituted by a succession of layers arranged around an inert, spherical core prepared from sugar and starch.

The composition of the present invention in the dosage form comprises :

(1) An inert core
(2) An active coating
(3) An intermediate coating and
(4) An enteric coating

The inert cores are constituted by pharmaceutically acceptable inert excipients and which are coated with a layer containing at least one benzimidazole in micronised form (omeprazole, lansoprazole, pantoprazole or rabeprazole), or their salts or their mixtures, mixed with pharmaceutically acceptable inert excipients, so that this layer quickly disaggregates. This drug layer is covered by intermediate coating comprising of a neutral

film-forming agent and finally this layer is coated with an enteric coating. The pellets have spherical symmetry and have a moisture level that guarantees good stability under normal storage conditions. The pellets are placed in hard gelatine capsules and it is in this form that they are administered to patients.

Accordingly, the present invention provides an improved stable pharmaceutical composition containing substituted benzimidazoles useful for the treatment of gastric and duodenal ulcers in the form of gelatine capsules which comprises

I. An inert core comprising of sugar and starch

II. The inert core having a coating of an active coating comprising at least one benzimidazole or its salts or their mixtures in micronised form with an inert pharmaceutically acceptable film forming agent and inert non-acidic / non-alkaline pharmaceutical excipients.

III. The resulting product having a coating of an intermediate coating comprising the same film forming agent as used for the coating of the inert core and the same inert non-acidic / non-alkaline pharmaceutical excipients.

IV. The resulting product having an enteric coating of a mixture of an enteric polymer, plasticizer and anti-adherent.

According to another feature of the present invention there is provided a process for the preparation of an improved and stable pharmaceutical composition useful for treating gastric and deuodonal ulcers which comprises

I. Forming an inert core comprising of sugar and starch in the form of spherical or nearly spherical pellets.

II. Providing to the inert core a coating of an active coating comprising of at least one benzimidazole or its salts or their mixtures in micronised form, an inert

pharmaceutically acceptable film forming agent and inert non-acidic / non-alkaline pharmaceutical excipients.

III. Providing the resulting spherical or nearly spherical pellets with an intermediate coating comprising of the same film forming agent as used in step (ii) above and the same inert non-acidic / non-alkaline pharmaceutical excipients.

IV. Providing to the resulting spherical or nearly spherical pellets with an yet another coating of an enteric coating layer comprising of a mixture of an enteric polymer, plasticizer and anti-adherent.

The sugar used for the inner core may consist of sugars such as sucrose, mannitol, lactose and the like. The core may be formed in a spherical or nearly spherical shape pellets. The amount of sugars and starch may range from 150.0 mg to 800.0 mg and 100.0mg to 600.0 mg per gram of composition preferably may range from 200.0 mg to 600.0 mg and 150.0 mg to 500.0 mg.

The active pharmaceutical agents employed may be selected from benzimadazole derivatives such as omeprazole, lansoprazole, pantoprazole, rabeprazole and their salts or their mixtures thereof. The amount of active drug may range from 30 .0 mg to 200.0 mg preferably may range from 50.0 mg to 150.0 mg per gram of the composition.

The film forming agent used in the active coating for binding the active pharmaceutical ingredient to the inert core is selected from cellulose derivatives such as hydroxypropyl cellulose, hydroxypropyl methylcellulose, sodium carboxy methyl cellulose, carboxy methyl cellulose and polyvinyl pyrrolidone derivatives and alginate derivatives or a

mixture thereof. The amount of film forming agent may range from 20.0 mg to 200.0 mg preferably may range from 25.0 mg to 150.0 mg per gram of composition.

The excipients when used in the active coating may be selected from materials such as microcrystalline cellulose powder, dicalcium phosphate, sodium lauryl sulphate, dioctyl sodium sulpho succinate, alginic acid, talc, magnesium stearate, titanium dioxide, starch and a mixture thereof and the coating solvent employed for active coating is purified water. The amount of the excipient may range from 0.2 mg to 100.0 mg preferably may range from 1.0mg to 80.0 mg per gram of composition.

The intermediate coating consists of a film forming agent. The film forming agent is selected from cellulose derivatives such as hydroxypropyl cellulose, hydroxypropyl methylcellulose, sodium carboxy methyl cellulose, carboxy methylcellulose, polyvinyl pyrrolidone derivatives and alginate derivatives or a mixture thereof. The amount of the film forming agent may range from 20.0 mg to 200.0 mg preferably may range from 25.0 mg to 150.0 mg per gram of composition.

The intermediate cores may also contain a excipient. The excipients used may be selected from materials such as microcrystalline cellulose powder, di-calcium phosphate, sodium lauryl sulphate, dioctyl sodium sulfosuccinate, alginic acid, talc, magnesium stearate, titanium dioxide, starch, etc or a mixture thereof. The amount of excipient employed may range from 2.0 mg to 100.0 mg preferably may range from 3.0 mg to 80.0 mg per gram.

The polymer used for the enteric coating of the composition may be those such as cellulose derivatives or methacrylic acid derivatives or the mixture thereof. The enteric

polymeric composition also contains plasticizer and anti-adherents. Further it may also optionally contain colorants and opacifiers.

The amount of polymer employed for the enteric coating may range from 20.0 mg to 300.0 mg preferably may range from 50.0 mg to 250.0 mg per gram of composition.

The cellulose derivatives used in the enteric coating may be selected from materials such as Cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate and methacrylic acid derivatives such as Eudragit L 100 – 55, Eudragit L 30D-55.

The plasticizer used may be selected from materials such as fatty alcohol derivatives such as cetyl alcohol, stearyl alcohol or phthalate derivatives such as diethyl phthalate, dipropyl phthalate, dibutyl phthalate, dioctyl phthalate or polyethelene glycol derivatives. The amount of plasticizer employed for enteric coating may range from 1.0 mg to 60.0 mg, preferably may range from 2.0 mg to 50.0 mg per gram of composition.

The anti-adherents used in the enteric coating may be selected from materials such as talc, stearate, stearic acid, hydrogenated castor oil or the mixture thereof. The colorants and opacifiers may be selected from iron oxides, titanium dioxide, or mixture thereof.

The amount of anti-adherents if employed may range from 2.0 mg to 120.0 mg, preferably may range from 4.0 mg to 100.0 mg per gram of composition.

The amount of opacifiers may range from 0.1 mg to 40.0 mg preferably may range from 0.5 to 30.0 mg per gram of composition

The solvent used for enteric coating may be selected from aqueous or organic solvents or mixture thereof. The aqueous solvents used may be purified water and the organic

solvents such as isopropyl alcohol, acetone, ethanol or mixture thereof may be used. They are present in traces after processing is completed.

The composition is made in the form of pellets, which are then filled, into hard gelatin capsules of suitable size depending upon the assay and required therapeutic dose of the drug.

Sugar spheres may be used as fillers or excipients to adjust the fill weight of the capsules. The invention is explained in detail in the Examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

The hard gelatin capsules comes in various sizes such as 00, 0, 1, 2, 3, etc., to accommodate various amounts of the composition. In the example 1 given below , for 20 mg of omeprazole size 2 is selected as capsule size for holding the composition , namely 20 mg of omeprazole is distributed over a number of coated pellets, before filling into the capsule, we need to analyse the coated pellets to find out how many of these coated pellets shall be filled into size 2 capsule to achieve 20mg of omeprazole . similar explantion holds good for other capsule sizes described in other examples also.

Example 1

Ingredients Active coating	Quantity (mg/gm)
Sugar spheres	490.00
Omeprazole	90.00
Hydroxypropyl Methylcellulose E5	50.00
Dicalcium phosphate	40.00
Dioctyl sodium sulpho succinate	30.00

Talc	5.00
Titanium dioxide	2.00
Purified water	q.s

Intermediate coating

Hydroxypropyl Methylcellulose E5	25.00
Dicalcium Phosphate	20.00
Dioctyl sodium sulpho succinate	1.00
Talc	30.00
Titanium dioxide	2.00
Purified water	q.s

Enteric coating

Hydroxypropyl Methylcellulose Phthalate	120.00
Cetyl alcohol	24.00
Diethyl phthalate	12.00
Talc	54.00
Titanium dioxide	5.00
Isopropyl alcohol	q.s
Acetone	q.s

Manufacturing Procedure :

A. Active coating

Hydroxypropyl Methylcellulose E5 and dioctyl sodium sulpho succinate were dissolved in water and the micronised mixture of omeprazole , dicalcium phosphate, talc and titanium dioxide were added to it with continuous stirring. A perforated coating pan was loaded with the sugar spheres and the drug suspension prepared as described above was sprayed on to the sugar spheres. The resulting pellets were dried in the perforated coating pan to a moisture content below 2% w/w.

B. **Intermediate coating**

Hydroxypropyl Methylcellulose E5 and dioctyl sodium sulpho succinate were dissolved in water and dicalcium phosphate was added to it. Talc and titanium dioxide were sifted

through 200# and added to the polymer solution with continuous stirring. A perforated coating pan was loaded with the active coating pellets prepared and described as above and the intermediate coating dispersion was applied on to the pellets. The resulting pellets were dried in a coating pan to a moisture content below 2% w/w.

C. **Enteric coating**

Diethyl phthalate and cetyl alcohol were dissolved in a solvent blend of Isopropyl alcohol and acetone followed by Hydroxypropyl Methylcellulose phthalate . Talc and titanium dioxide were sifted through 200# and added to the polymer solution. The intermediate coated pellets prepared as described as above were loaded in fluid bed coater and the enteric coating dispersion was applied on to these pellets. The pellets were then dried to a moisture content below 2% w/w.

The enteric coated pellets are filled into hard gelatin capsules size "2" after dilution with sugar spheres, to obtain the dose of 20mg of Omeprazole., depending on the assay

Example 2

Ingredients	Quantity(mg/gm)
a) Active coating	
Sugar spheres	481.00
Omeprazole	86.00
Hydroxypropyl Methylcellulose E5	60.00
Microcrystalline cellulose powder	50.00
Sodium Lauryl sulphate	10.00
Titanium dioxide	4.00
Talc	5.00
Purified water	q.s
b) **Intermediate coating**	
Hydroxypropyl Methylcellulose E5	50.00
Microcrystalline cellulose powder	42.00

Sodium lauryl sulphate	5.00
Titanium dioxide	2.00
Talc	3.00
Purified water	q.s

c) **Enteric coating**

Hydroxypropyl Methylcellulose phthalate	120.00
Cetyl alcohol	24.00
Diethyl phthalate	12.00
Talc	36.00
Titanium dioxide	10.00
Isopropyl alcohol	q.s
Acetone	q.s

Manufacturing Procedure :

A. Active coating

Hydroxypropyl Methylcellulose E5 and sodium lauryl sulphate were dissolved in water and the micronised mixture of omeprazole , microcrystalline cellulose powder and titanium dioxide and talc were added to it with continuous stirring. A perforated coating pan was loaded with the sugar spheres and the drug suspension was sprayed on to the sugar spheres. The pellets were dried in the perforated coating pan to a moisture content below 2% w/w.

B. Intermediate coating

Hydroxypropyl Methylcellulose E5 and sodium lauryl sulphate were dissolved in water. Microcrystalline cellulose powder , titanium dioxide and talc were sifted through 200# and added to the polymer solution with continuous stirring. A perforated coating Pan was loaded with the active coated pellets and the intermediate coating dispersion was applied on to the pellets. The resulting pellets were dried in the perforated coating pan to a moisture content below 2% w/w.

C. Enteric coating

Diethyl phthalate and cetyl alcohol were dissolved in a solvent blend of isopropyl alcohol and acetone followed by Hydroxypropyl Methylcellulose phthalate. Talc and titanium dioxide were sifted through 200# and added to the polymer solution. The intermediate coated pellets prepared as described above were loaded in a perforated coating pan and the enteric coating dispersion was applied on to these pellets. The resulting pellets were dried to a moisture content below 2% w/w.

The enteric coated pellets are filled into hard gelatin capsules size "0" after dilution with sugar spheres, to obtain the dose of 40 mg of Omeprazole., depending on the assay .

Example 3

Ingredients	Quantity(mg/gm)
a. **Active coating**	
Sugar spheres	400.00
Omeprazole	85.00
Hydroxypropyl Methylcellulose E5	55.00
Starch	40.00
Magnesium Stearate	25.00
Dioctyl sodium sulpho succinate	8.00
Titanium dioxide	3.00
Purified water	q.s
b. **Intermediate coating**	
Hydroxypropyl Methylcellulose E5	25.00
Starch	18.00
Magnesium Stearate	11.00
Dioctyl sodium sulpho succinate	2.00
Titanium dioxide	4.00
Purified water	q.s
c. **Enteric coating**	
Eudragit L-30D-55	720mg of dispersion eq. To 240.00mg of solids

Polyethylene glycol 6000	12.00
Talc	45.00
Titanium dioxide	15.00
Triethyl citrate	12.00
Purified Water	q.s

Manufacturing Procedure :

A. Active coating

Hydroxypropyl Methylcellulose E5 and dioctyl sodium sulpho succinate were dissolved in water and the micronised mixture of omeprazole , starch, magnesium stearate and titanium dioxide were added to it with continuous stirring. A fluidbed coater was loaded with the sugar spheres and the drug suspension was sprayed on to the sugar spheres. The resulting pellets were dried in the fluidbed coater to a moisture content below 2% w/w.

B. Intermediate coating

Hydroxypropyl Methylcellulose E5 and dioctyl sodium sulpho succinate were dissolved in water. Titanium dioxide , starch and magnesium stearate were sifted through 200# and added to the polymer solution with continuous stirring. A fluid bed coater was loaded with the active coated pellets and the intermediate coating dispersion was applied on to these pellets. The resultant pellets were dried in the fluidbed coater to a moisture content below 2% w/w.

C. Enteric coating

Polyethlene glycol 6000 was dissolved in water and added to Eudragit L-30D-55 dispersion with continuous stirring and added triethyl citrate. Talc and titanium dioxide were sifted through 200# and added to the polymer solution with continuous stirring. The intermediate coated pellets were loaded in fluid bed coater and the enteric coating dispersion was applied on to the pellets. The resulting pellets were dried to a moisture content below 2% w/w.

The enteric coated pellets are filled into hard gelatin capsules size "2" after dilution with sugar spheres, to obtain the dose of 20mg of Omeprazole., depending on the assay

Example 4

Ingredients	Quantity(mg/gm)

a) **Active coating**

Sugar spheres	490.00
Lansoprazole	90.00
Hydroxypropyl Methylcellulose E5	50.00
Dicalcium phosphate	40.00
Dioctyl sodium sulpho succinate	30.00
Talc	5.00
Titanium dioxide	2.00
Purified water	q.s

b) **Intermediate coating**

Hydroxypropyl Methylcellulose E5	25.00
Dicalcium Phosphate	20.00
Dioctyl sodium sulpho succinate	1.00
Talc	30.00
Titanium dioxide	2.00
Purified water	q.s

c) **Enteric coating**

Hydroxypropyl Methylcellulose Phthalate	120.00
Cetyl alcohol	24.00
Diethyl phthalate	12.00
Talc	54.00
Titanium dioxide	5.00
Isopropyl alcohol	q.s
Acetone	q.s

Manufacturing Procedure :

A. Active Coating

Hydroxypropyl Methylcellulose E5 and dioctyl sodium sulpho succinate were dissolved in water and the micronised mixture of Lansoprazole , dicalcium phosphate, talc and titanium dioxide were added to it with continuous stirring. A perforated coating pan was loaded with the sugar spheres and the drug suspension on to the sugar spheres was

sprayed on to the sugar spheres. The resulting pellets were dried in the perforated coating pan to a moisture content reached below 2% w/w.

B. **Intermediate coating**

Hydroxypropyl Methylcellulose E5 and dioctyl sodium sulpho succinate were dissolved in water and dicalcium phosphate was added to it. Talc and titanium dioxide were sifted through 200# and added to the polymer solution with continuous stirring. A perforated coating pan was loaded with the active coated pellets and the intermediate coating dispersion was applied on to the pellets. The resulting pellets were dried in the perforated coating pan to a moisture content below 2% w/w.

c.**Enteric coating**

Diethyl phthalate and cetyl alcohol were dissolved in a solvent blend of Isopropyl alcohol and acetone followed by Hydroxypropyl Methylcellulose phthalate . Talc and titanium dioxide were sifted through 200# and added to the polymer solution. The intermediate coated pellets were loaded in a perforated coating pan and the enteric coating dispersion was applied on to these pellets. The resulting pellets were dried to a moisture content below 2% w/w.

The enteric coated pellets are filled into hard gelatin capsules size "3" after dilution with sugar spheres, to obtain the dose of 15 mg of Lansoprazole ., depending on the assay.

Example 5

Ingredients	Quantity(mg/gm)
a) **Active Coating**	
Sugar spheres	481.00
Lansoprazole	86.00
Hydroxypropyl Methylcellulose E5	60.00
Microcrystalline cellulose powder	50.00

Sodium Lauryl sulphate	10.00
Titanium dioxide	4.00
Talc	5.00
Purified water	q.s

b) **Intermediate coating**

Hydroxypropyl Methylcellulose E5	50.00
Microcrystalline cellulose powder	42.00
Sodium lauryl sulphate	5.00
Titanium dioxide	2.00
Talc	3.00
Purified water	q.s

c) **Enteric coating**

Hydroxypropyl Methylcellulose phthalate	120.00
Cetyl alcohol	24.00
Diethyl phthalate	12.00
Talc	36.00
Titanium dioxide	10.00
Isopropyl alcohol	q.s
Acetone	q.s

Manufacturing Procedure :

a) **Active Coating**

Hydroxypropyl Methylcellulose E5 and sodium lauryl sulphate were dissolved in water and the micronised mixture of Lansoprazole , microcrystalline cellulose powder and titanium dioxide and talc were added to it with continuous stirring. A perforated coating pan was loaded with the sugar spheres and the drug suspension was sprayed on to the sugar spheres. The resulting pellets were dried in the perforated coating pan to a moisture content below 2% w/w.

B. Intermediate coating

Hydroxypropyl Methylcellulose E5 and sodium lauryl sulphate were dissolved in water. Microcrystalline cellulose powder , titanium dioxide and talc were sifted through 200# and added to the polymer solution with continuous stirring. A perforated coating pan was loaded with the active coated pellets and the intermediate coating dispersion was applied on the pellets. The resulting pellets were dried in the perforated coating pan to a moisture content below 2% w/w.

C. Enteric coating

Diethyl phthalate and cetyl alcohol were dissolved in a solvent blend of isopropyl alcohol and acetone followed by Hydroxypropyl Methylcellulose phthalate. Talc and titanium dioxide sifted through 200# and added to the polymer solution. The intermediate coated pellets were loaded in fluid bed coater and the enteric coating dispersion was applied on to these pellets. The resulting pellets were dried till the moisture content reached below 2% w/w.

The enteric coated pellets are filled into hard gelatin capsules size " 1 " after dilution with sugar spheres, to obtain the dose of 30 mg of Lansoprazole., depending on the assay.

Example 6

Ingredients	Quantity(mg/gm)
a) Active Coating	
Sugar spheres	400.00
Lansoprazole	85.00
Hydroxypropyl Methylcellulose E5	55.00
Starch	40.00
Magnesium Stearate	25.00
Dioctyl sodium sulpho succinate	8.00
Titanium dioxide	3.00
Purified water	q.s
b) Intermediate coating	
Hydroxypropyl Methylcellulose E5	25.00

Starch	18.00
Magnesium Stearate	11.00
Dioctyl sodium sulpho succinate	2.00
Titanium dioxide	4.00
Purified water	q.s

c) Enteric coating

Eudragit L-30D-55	720mg of dispersion eq. To 240.00mg of solids
Polyethylene glycol 6000	12.00
Talc	45.00
Titanium dioxide	15.00
Triethyl citrate	12.00
Purified Water	q.s

Manufacturing Procedure :

A. Active Coating

Hydroxypropyl Methylcellulose E5 and dioctyl sodium sulpho succinate were dissolved in water and the micronised mixture of Lansoprazole , starch, magnesium stearate and titanium dioxide were added to it with continuous stirring. A fluid bed coater was loaded with the sugar spheres and the drug suspension was sprayed on to the sugar spheres. The resulting pellets were dried in the coating pan to a moisture content below 2% w/w.

B. Intermediate coating

Hydroxypropyl Methylcellulose E5 and dioctyl sodium sulpho succinate were dissolved in water. Titanium dioxide , starch and magnesium stearate were sifted through 200# and added to the polymer solution with continuous stirring. A fluid bed coater was loaded with the active coated pellets and the intermediate coating dispersion was applied on to the pellets. The resulting pellets were dried in the coating pan to a moisture content below 2% w/w.

C. Enteric coating

Polyethlene glycol 6000 was dissolved in water and added to Eudragit L-30D-55 dispersion with continuous stirring and triethyl citrate was added to it . Talc and titanium dioxide were shifted through 200# and added to the polymer solution with continuous stirring. The intermediate coated pellets were loaded in fluid bed coater and the enteric coating dispersion was applied on these pellets. The resulting pellets were dried in a coating pan to a moisture content below 2% w/w.

The enteric coated pellets are filled into hard gelatin capsules size "1" after dilution with sugar spheres, to obtain the dose of 30 mg of Lansoprazole., depending on the assay.

Example 7

Ingredients	Quantity(mg/gm)
a) Active Coating	
Sugar spheres	490.00
Pantoprazole sodium	90.00
Hydroxypropyl Methylcellulose E5	50.00
Dicalcium phosphate	40.00
Dioctyl sodium sulpho succinate	30.00
Talc	5.00
Titanium dioxide	2.00
Purified water	q.s
b) **Intermediate coating**	
Hydroxypropyl Methylcellulose E5	25.00
Dicalcium Phosphate	20.00
Dioctyl sodium sulpho succinate	1.00
Talc	30.00
Titanium dioxide	2.00
Purified water	q.s
c) Enteric coating	
Hydroxypropyl Methylcellulose Phthalate	120.00
Cetyl alcohol	24.00
Diethyl phthalate	12.00

Talc	54.00
Titanium dioxide	5.00
Isopropyl alcohol	q.s
Acetone	q.s

Manufacturing Procedure :

A. Active coating

Hydroxypropyl Methylcellulose E5 and dioctyl sodium sulpho succinate were dissolved in water and the micronised mixture of Pantoprazole sodium , dicalcium phosphate, talc and titanium dioxide were added to it with continuous stirring. A perforated coating pan was loaded with the sugar spheres and the drug suspension was sprayed on to the sugar spheres. The resulting pellets were dried in the perforated coating pan to a moisture content below 2% w/w.

B. Intermediate coating

Hydroxypropyl Methylcellulose E5 and dioctyl sodium sulpho succinate were dissolved in water and dicalcium phosphate was added to it. Talc and titanium dioxide were sifted through 200# and added to the polymer solution with continuous stirring. A perforated coating pan was loaded with the active coated pellets and the intermediate coating dispersion was applied on to the pellets. The resulting pellets were dried in the perforated coating pan to a moisture content below 2% w/w.

C. Enteric coating

Diethyl phthalate and cetyl alcohol were dissolved in a solvent blend of Isopropyl alcohol and acetone followed by Hydroxypropyl Methylcellulose phthalate . Talc and titanium dioxide were sifted through 200# and added to the polymer solution. The intermediate coated pellets were loaded in fluid bed coater and the enteric coating dispersion was applied on to these pellets. The resulting pellets were dried to a moisture content below 2% w/w.

The enteric coated pellets are filled into hard gelatin capsules size "1" after dilution with sugar spheres, to obtain the dose of 40 mg of Pantoprazole., depending on the assay.

Example 8

Ingredients	Quantity(mg/gm)
a) Active Coating	
Sugar spheres	481.00
Pantoprazole sodium	86.00
Hydroxypropyl Methylcellulose E5	60.00
Microcrystalline cellulose powder	50.00
Sodium Lauryl sulphate	10.00
Titanium dioxide	4.00
Talc	5.00
Purified water	q.s
b) Intermediate coating	
Hydroxypropyl Methylcellulose E5	50.00
Microcrystalline cellulose powder	42.00
Sodium lauryl sulphate	5.00
Titanium dioxide	2.00
Talc	3.00
Purified water	q.s
c) Enteric coating	
Hydroxypropyl Methylcellulose phthalate	120.00
Cetyl alcohol	24.00
Diethyl phthalate	12.00
Talc	36.00
Titanium dioxide	10.00
Isopropyl alcohol	q.s
Acetone	q.s

Manufacturing Procedure :

A. Active Coating

Hydroxypropyl Methylcellulose E5 and sodium lauryl sulphate were dissolved in water and the micronised mixture of Pantoprazole sodium , microcrystalline cellulose powder , titanium dioxide and talc was added to it with continuous stirring. A perforated coating pan was loaded with the sugar spheres and the drug suspension was applied on to the sugar spheres. The resulting pellets are dried in the perforated coating pan to a moisture content below 2% w/w.

B. Intermediate coating

Hydroxypropyl Methylcellulose E5 and sodium lauryl sulphate were dissolved in water. Microcrystalline cellulose powder and titanium dioxide were sifted through 200# and added to the polymer solution with continuous stirring. A fluid bed coater was loaded with the active coated pellets and the intermediate coating dispersion was applied on to the pellets. The resulting pellets are dried in the fluid bed coater to a moisture content below 2% w/w.

C) Enteric coating

Diethyl phthalate and cetyl alcohol were dissolved in a solvent blend of isopropyl alcohol and acetone followed by Hydroxypropyl Methylcellulose phthalate. Talc and titanium dioxide were sifted through 200# and added to the polymer solution. The intermediate coatinged pellets were loaded in fluid bed coater and the enteric coating dispersion was applied on to these pellets . The resulting pellets were dried to a moisture content below 2% w/w.

The enteric coated pellets are filled into hard gelatin capsules size "2" after dilution with sugar spheres, to obtain the dose of 20 mg of Pantoprazole., depending on the assay.

Example 9

Ingredients	Quantity(mg/gm)
A) Active Coating	
Sugar spheres	400.00
Pantoprazole sodium	85.00
Hydroxypropyl Methylcellulose E5	55.00
Starch	40.00

Magnesium Stearate	25.00
Dioctyl sodium sulpho succinate	8.00
Titanium dioxide	3.00
Purified water	q.s

B) Intermediate coating

Hydroxypropyl Methylcellulose E5	25.00
Starch	18.00
Magnesium Stearate	11.00
Dioctyl sodium sulpho succinate	2.00
Titanium dioxide	4.00
Purified water	q.s

C) Enteric coating

Eudragit L-30D-55	720mg of dispersion eq. To 240.00mg of solids
Polyethylene glycol 6000	12.00
Talc	45.00
Titanium dioxide	15.00
Triethyl citrate	12.00
Purified Water	q.s

Manufacturing Procedure :

A. Active Coating

Hydroxypropyl Methylcellulose E5 and dioctyl sodium sulpho succinate were dissolved in water and the micronised mixture of Pantoprazole sodium , starch, magnesium stearate and titanium dioxide were added to it with continuous stirring. A perforated coating pan was loaded with the sugar spheres and the drug suspension was sprayed on to the sugar spheres. The pellets were dried in the coating pan to a moisture content below 2% w/w.

B. Intermediate coating

Hydroxypropyl Methylcellulose E5 and dioctyl sodium sulpho succinate were dissolved in water. Titanium dioxide , starch and magnesium stearate were sifted through 200# and

added to the polymer solution with continuous stirring. A perforated coating pan was loaded with the active coated pellets and the intermediate coating dispersion was applied on to the pellets. The resulting pellets were dried in the coating pan to a moisture content below 2% w/w.

C. Enteric coating

Polyethlene glycol 6000 was dissolved in water and added to Eudragit L-30D-55 dispersion with continuous stirring and added triethyl citrate. Talc and titanium dioxide were sifted through 200# and added to the polymer solution with continuous stirring. The intermediate coated pellets were loaded in a perforated coating pan and the enteric coating dispersion was applied on to these pellets. The resulting pellets were dried to a moisture content below 2% w/w.

The enteric coated pellets are filled into hard gelatin capsules size "1" after dilution with sugar spheres, to obtain the dose of 40 mg of Pantoprazole., depending on the assay.

Example 10

Ingredients	Quantity(mg/gm)
A) Active Coating	
Sugar spheres	490.00
Rabeprazole sodium	90.00
Hydroxypropyl Methylcellulose E5	50.00
Dicalcium phosphate	40.00
Dioctyl sodium sulpho succinate	30.00
Talc	5.00
Titanium dioxide	2.00
Purified water	q.s
B) Intermediate coating	
Hydroxypropyl Methylcellulose E5	25.00
Dicalcium Phosphate	20.00
Dioctyl sodium sulpho succinate	1.00

Talc	30.00
Titanium dioxide	2.00
Purified water	q.s

C) Enteric coating

Hydroxypropyl Methylcellulose Phthalate	120.00
Cetyl alcohol	24.00
Diethyl phthalate	12.00
Talc	54.00
Titanium dioxide	5.00
Isopropyl alcohol	q.s
Acetone	q.s

Manufacturing Procedure :

A. Active Coating

Hydroxypropyl Methylcellulose E5 and dioctyl sodium sulpho succinate were dissolved in water and the micronised mixture of Rabeprazole sodium , dicalcium phosphate, talc and titanium dioxide was added to it with continuous stirring. A perforated coating pan was loaded with the sugar spheres and the drug suspension was sprayed on to the sugar spheres. The resulting pellets were dried in the perforated coating pan to a moisture content below 2% w/w.

B. Intermediate coating

Hydroxypropyl Methylcellulose E5 and dioctyl sodium sulpho succinate were dissolved in water and added dicalcium phosphate. Talc and titanium dioxide were sifted through 200# and added to the polymer solution with continuous stirring. A perforated coating pan was loaded with the active coated pellets and the intermediate coating dispersion was applied on to the pellets. The resulting pellets were dried in the perforated coating pan to a moisture content below 2% w/w.

C. Enteric coating

Diethyl phthalate and cetyl alcohol were dissolved in a solvent blend of Isopropyl alcohol and acetone followed by Hydroxypropyl Methylcellulose phthalate . Talc and titanium dioxide were sifted through 200# and added to the polymer solution. The intermediate coated pellets were loaded in the perforated coating pan and the enteric coating dispersion was applied on to these pellets. The resulting pellets were dried to a moisture content below 2% w/w.

The enteric coated pellets are filled into hard gelatin capsules size "2" after dilution with sugar spheres, to obtain the dose of 20 mg of Rabeprazole., depending on the assay.

Example 11

Ingredients	Quantity(mg/gm)
A) Active Coating	
Sugar spheres	481.00
Rabeprazole sodium	86.00
Hydroxypropyl Methylcellulose E5	60.00
Microcrystalline cellulose powder	50.00
Sodium Lauryl sulphate	10.00
Titanium dioxide	4.00
Talc	5.00
Purified water	q.s
B) Intermediate coating	
Hydroxypropyl Methylcellulose E5	50.00
Microcrystalline cellulose powder	42.00
Sodium lauryl sulphate	5.00
Titanium dioxide	2.00
Talc	3.00
Purified water	q.s
C) Enteric coating	
Hydroxypropyl Methylcellulose phthalate	120.00
Cetyl alcohol	24.00

Diethyl phthalate	12.00
Talc	36.00
Titanium dioxide	10.00
Isopropyl alcohol	q.s
Acetone	q.s

Manufacturing Procedure :

A. Active Coating

Hydroxypropyl Methylcellulose E5 and sodium lauryl sulphate were dissolved in water and the micronised mixture of Rabeprazole sodium , microcrystalline cellulose powder , titanium dioxide and talc was added to it with continuous stirring. A perforated coating pan was loaded with the sugar spheres and the drug suspension was sprayed on to the sugar spheres. The resulting pellets were dried in the perforated coating pan to a moisture content below 2% w/w.

B. **Intermediate coating**

Hydroxypropyl Methylcellulose E5 and sodium lauryl sulphate were dissolved in water. Microcrystalline cellulose powder , titanium dioxide and talc were sifted through 200# and added to the polymer solution with continuous stirring. A fluid bed coater was loaded with the active coated pellets and the intermediate coating dispersion was applied on to the pellets. The resulting pellets were dried in the fluid bed coater to a moisture content below 2% w/w.

C. Enteric coating

Diethyl phthalate and cetyl alcohol were dissolved in a solvent blend of isopropyl alcohol and acetone followed by Hydroxypropyl Methylcellulose phthalate. Talc and titanium dioxide were sifted through 200# and added to the polymer solution. The intermediate coated pellets were loaded in fluid bed coater and the enteric coating dispersion was applied on to these pellets. The resulting pellets were dried to a moisture content below 2% w/w.

The enteric coated pellets are filled into hard gelatin capsules size "2" after dilution with sugar spheres, to obtain the dose of 20 mg of Rabeprazole., depending on the assay.

Example 12

Ingredients	Quantity(mg/gm)
A) Active Coating	
Sugar spheres	400.00
Rabeprazole sodium	85.00
Hydroxypropyl Methylcellulose E5	55.00
Starch	40.00
Magnesium Stearate	25.00
Dioctyl sodium sulpho succinate	8.00
Titanium dioxide	3.00
Purified water	q.s
B) Intermediate coating	
Hydroxypropyl Methylcellulose E5	25.00
Starch	18.00
Magnesium Stearate	11.00
Dioctyl sodium sulpho succinate	2.00
Titanium dioxide	4.00
Purified water	q.s
C) Enteric coating	
Eudragit L-30D-55	720mg of dispersion eq. To 240.00mg of solids
Polyethylene glycol 6000	12.00
Talc	45.00
Titanium dioxide	15.00
Triethyl citrate	12.00
Purified Water	q.s

Manufacturing Procedure :

A. Active Coating

Hydroxypropyl Methylcellulose E5 and dioctyl sodium sulpho succinate were dissolved in water and the micronised mixture of Rabeprazole sodium , starch, magnesium stearate and titanium dioxide was added to it with continuous stirring. A fluid bed coater was loaded with the sugar spheres and the drug suspension was sprayed on to the sugar spheres. The resulting pellets were dried in the fluid bed coater to the moisture content below 2% w/w.

B. Intermediate coating

Hydroxypropyl Methylcellulose E5 and dioctyl sodium sulpho succinate were dissolved in water. Titanium dioxide , starch and magnesium stearate were sifted through 200# and added to the polymer solution with continuous stirring. A fluid bed coater pan was loaded with the active coated pellets and the intermediate coating dispersion was applied on to the pellets. The resulting pellets were dried in the fluid bed coater to a moisture content below 2% w/w.

C. Enteric coating

Polyethlene glycol 6000 was dissolved in water and added to Eudragit L-30D-55 dispersion with continuous stirring and added triethyl citrate. Talc and titanium dioxide were sifted through 200# and added to the polymer solution with continuous stirring. The intermediate coated pellets were loaded in fluid bed coater and the enteric coating dispersion was applied on to these pellets. The resulting pellets were dried to a moisture content below 2% w/w.

The enteric coated pellets are filled into hard gelatin capsules size "2" after dilution with sugar spheres, to obtain the dose of 20 mg of Rabeprazole., depending on the assay.

Advantages of the present invention:

1. The composition is stable.
2. The composition does not employ any alkali agent.
3. The composition is simple, commercially viable, economical and highly reproduceable.

4. All the materials used in the composition , particularly those used for preparing the active coating and intermediate coating are biocompatible, widely available, pharmaceutically inert, economical and have a high degree of safety.
5. The active ingredient is not released in the stomach but released only in the intestine (namely in an alkaline environment). In other words, the composition is protected in the acidic environment of the gastric system and is released in the alkaline environment of the intestinal system.
6. The pellets can be processed in any type of available equipments , for example , from the perforated coating pan to automatic fluidised bed pelletisation and coating equipments making the preparation of the composition simple and versatile.
7. The pellets can be processed free from organic solvents thereby making it safe to handle for operational staff as it is non hazardous.
8. The process does not create pollution ie it is environmentally safe .

We claim,

1. An improved stable pharmaceutical composition containing substituted benzimidazoles useful for the treatment of gastric and duodenal ulcers in the form of hard gelatine capsules which comprises

(a) An inert core comprising of sugar and starch.

(b) The inert core having a coating of an active coating comprising at least one benzimidazole or its salts or their mixtures in micronised form with an inert pharmaceutically acceptable film forming agent with inert non-acidic / non-alkaline pharmaceutical excipients.

(c) The resulting product having a coating of an intermediate coating comprising the same film forming agent as used for the coating of the inert core and inert non-acidic / non-alkaline pharmaceutical excipients.

(d) The resulting product having an enteric coating of a mixture of an enteric polymer, plasticizer and anti-adherents in a solvent base.

2. An improved pharmaceutical composition as claimed in claim 1 wherein the inert core comprises of sugars such as sucrose, mannitol, lactose and the like.

3. An improved pharmaceutical composition as claimed in claims 1 and 2 wherein the amount of sugars and starch present in the composition ranges from 150.0 mg to 800.0 mg and 100.0 mg to 600.0 mg per gram of composition., more preferably from 200.0 mg to 600.0 mg and 150.0 mg to 500.0 mg.

4. An improved pharmaceutical composition as claimed in claims 1 to 3 wherein the active pharmaceutical agents employed are selected from benzimadazole derivatives. selected from omeprazole, lansoprazole, pantoprazole, and rabeprazole and the salts thereof or a mixture thereof.

5. An improved pharmaceutical composition as claimed in claims 1 to 4 wherein the active pharmaceutical agent present in the active coat ranges from 30.0 mg to 200.0 mg and preferably from 50.0 mg to 150.0 mg per gram of the composition.

6. An improved pharmaceutical composition as claimed in claims 1 to 5 wherein the polymers used for making the active coating are selected from cellulose derivatives such as hydroxypropyl cellulose, hydroxypropyl methylcellulose, sodium carboxy methyl cellulose, carboxy methyl cellulose and polyvinyl pyrrolidone derivatives and alginate derivatives .

7. .An improved pharmaceutical composition as claimed in claim 6 wherein the cellulose derivatives such as hydroxypropyl methylcellulose having a molecular weight of 10000 to 150000, hydroxypropyl cellulose having a molecular weight of 80000 – 1150000, hydroxyethyl cellulose having a varying viscosities 2-20000 mpa or pyrrolidone derivatives having a K value of 10-120 and molecular weight ranging from 2500 to 3000000 are used.

8. .An improved pharmaceutical composition as claimed in claims 6 to 7 wherein the amount of the polymers employed range from 20.0 mg to 200.0 mg and preferably 25.0 mg to 150.0 mg per gram of composition.

9. An improved pharmaceutical composition as claimed in claims 1 to 8 wherein the active core contains excipients selected from materials such as microcrystalline cellulose powder, dicalcium phosphate, sodium lauryl sulphate, dioctyl sodium sulpho succinate, alginic acid, talc, titanium dioxide, starch and a mixture thereof.

10. An improved pharmaceutical composition as claimed in claim 9 wherein the amount of excipients employed range from 0.2 mg to 100.0 mg and preferably from 1.0 mg to 80.0 mg per gram of composition.

11. An improved pharmaceutical composition as claimed in claims 1 to 10 wherein the coating solvent employed for active coating is purified water.

12. .An improved pharmaceutical composition as claimed in claims 1 to 11 wherein the intermediate coating consists of a film forming agent and excipients.

13. .An improved pharmaceutical composition as claimed in claim 12 wherein the film forming agent are selected for intermediate coating is selected from cellulose derivatives such as hydroxypropyl cellulose, hydroxypropyl methylcellulose, sodium carboxy methyl cellulose, carboxy methyl cellulose and polyvinyl pyrrolidone derivatives and alginate derivatives.

14. An improved pharmaceutical composition as claimed in claims 1 to 14 wherein the cellulose derivatives used in making the intermediate coat are selected from hydroxypropyl methylcellulose having a molecular weight of 10000 to 150000, hydroxypropyl cellulose having a molecular weight of 80000 – 1150000, hydroxyethyl cellulose having a varying viscosities 2-20000 mpa or pyrrolidone derivatives having a K value of 10-120 and molecular weight ranging from 2500 to 3000000 are used.

15. An improved pharmaceutical composition as claimed in claim 14 wherein the amount of the film forming agent employed range from 20.0 mg to 200.0 mg and preferably 25.0 mg to 150.0 mg per gram of composition.

16. . An improved and stable pharmaceutical composition as claimed in claims 14 and 15 wherein it contains excipients selected from materials such as microcrystalline cellulose powder, dicalcium phosphate, sodium lauryl sulphate, dioctyl sodium sulpho succinate, alginic acid, talc, titanium dioxide, starch and a mixture thereof.

17. An improved and stable pharmaceutical composition as claimed in claims 14 to 16 wherein the amount of excipients employed ranges from 2.0 mg to 100.0 mg and preferably from 3.0 mg to 80.0 mg per gram of composition.

18. An improved and stable pharmaceutical composition as claimed in claims 1 to 17 wherein the coating solvent employed for making the intermediate coating is purified water.

19. An improved pharmaceutical composition as claimed in claims 1 to 18 wherein the enteric coating used for coating contains an enteric polymer such as cellulose derivatives or methacrylic acid derivatives or the mixture thereof.

20. .An improved pharmaceutical composition as claimed in claims 1 to 19 wherein the enteric polymeric composition also contains plasticizer and anti-adherents

21. An improved pharmaceutical composition as claimed in claims 1 to 20 wherein the enteric polymeric composition also contains, optionally, colorants and opacifiers.

22. An improved pharmaceutical composition as claimed in claims 1 to 21 wherein the cellulose derivatives such as Cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate and methacrylic acid derivatives such as Eudragit L 100 – 55 , Eudragit L 30D-55 are used.

23. An improved pharmaceutical composition as claimed in claims 1 to 22 wherein the amount of enteric polymer present in the enteric coating composition ranges from

20.0 mg to 300.0mg and preferably from 50.0 mg to 250.0mg per gram of composition.

24. An improved and stable pharmaceutical composition as claimed in claims 1 to 23 wherein the plasticizer used in the enteric coating is selected from materials such as fatty alcohol derivatives such as cetyl alcohol , stearyl alcohol or phthalate derivatives such as diethyl phthalate, dipropyl phthalate, dibutyl phthalate, dioctyl phthalate or polyethelene glycol derivatives having the molecular weight ranges of 200 to 10000 or a mixture thereof

25. An improved pharmaceutical composition as claimed in claims 1 to 24 wherein the amount of plasticizer used in the enteric coating ranges from 1.0 mg to 60.0mg , preferably from 2.0 mg to 50.0 mg per gram of composition.

26. An improved pharmaceutical composition as claimed in claims 1 to 25 wherein the anti-adherents used in the enteric coating is selected from materials such as talc, stearate, stearic acid, hydrogenated castor oil or the mixture thereof.

27. An improved pharmaceutical composition as claimed in claims 1 to 26 wherein the amount of anti adherents used ranges from 2.0 mg to 120.0 mg, preferably from 4.0 mg to 100.0 mg per gram of composition.

28. An improved pharmaceutical composition as claimed in claims 21 to 27 wherein the colorants and opacifiers used in the enteric coating is selected from iron oxides, titanium dioxide or mixture thereof.

29. An improved pharmaceutical composition as claimed in claim 28 wherein the amount of colorants and opacifiers, if present , ranges from 0.1mg to 40.0 mg ,preferably from 0.5 mg to 30.0 mg per gram of composition.

30. An improved pharmaceutical composition as claimed in claims 1 to 29 wherein the solvent used for enteric coating of the composition is selected from aqueous or organic solvents or mixture thereof.

31. An improved pharmaceutical composition as claimed in claim 30 wherein the aqueous solvent used is purified water and the organic solvents used is selected from Isopropyl alcohol, acetone, ethanol or mixture thereof.

32. An improved composition as claimed in claims 1 to 31 wherein the pellets are filled into hard gelatin capsules of suitable size depending upon the drug assay and required therapeutic dose of the drug.

33. An improved composition as claimed in claim 32 wherein the sugar spheres are used as fillers or excipients to adjust the fill weight of the capsule.

34. An improved composition as claimed in claim 33 wherein the amount of such sugar spheres may ranges from 1.0 mg to 150.0 mg, preferably 5.0 mg to 100.0 mg per capsule based on the assay of enteric coated pellets and fill weight of capsules.

35. According to another feature of the present invention there is provided a process for the preparation of an improved and stable pharmaceutical composition useful for treating gastric and deuodonal ulcers which comprises

(a) Forming an inert core comprising of sugar and starch in the form of spherical or nearly spherical pellets.

(b) Providing to the inert core a coating of an active coating comprising of at least one benzimidazole or its salts or their mixtures in micronised form, an inert pharmaceutically acceptable film forming agent and inert non-acidic / non-alkaline pharmaceutical excipients.

(c) Providing the resulting spherical or nearly spherical pellets with an intermediate coating comprising of the same film forming agent as used in step (ii) above and inert non-acidic / non-alkaline pharmaceutical excipients.

(d) Providing to the resulting spherical or nearly spherical pellets with an yet another coating of an enteric coating layer comprising of a mixture of an enteric polymer, plasticizer and anti-adherents in a solvent base

36. A process as claimed in claim 35 wherein the inert core consists of a mixture of starch and sugars such as sucrose, mannitol, and lactose.

37. A process as claimed in claimed in claims 35 and 36 wherein the amount of sugars and starch used ranges from 150.0 mg to 800.0 mg and 100.0 mg to 600.0 mg respectively, more preferably 200.0 mg to 600.0 mg and 150.0 mg to 500.0 mg respectively per gram of the composition.

38. A process as claimed in claims 35 to 37 wherein the active pharmaceutical agents employed are selected from benzimadazole derivatives selected from omeprazole, lansoprazole, pantoprazole, rabeprazole, and their salts or a mixture thereof.

39. A process as claimed in claims 35 to 38 wherein the active pharmaceutical agents present in the active coating ranges from 30.0 mg to 200.0 mg, preferably from 50.0 mg to 150.0 mg per gram of the composition.

40. A process as claimed in claims 35 to 39 wherein the film forming agent used in making the intermediate coating are selected from cellulose derivatives such as hydroxypropyl cellulose, hydroxypropyl methylcellulose, sodium carboxy methyl cellulose, carboxy methyl cellulose and polyvinyl pyrrolidone derivatives and alginate derivatives.

41. A process as claimed in claim 40 wherein the cellulose derivatives such as hydroxypropyl methylcellulose having a molecular weight of 10000 to 150000, hydroxypropyl cellulose having a molecular weight of 80000 – 1150000, hydroxyethyl cellulose having varying viscosities 2-20000 mpa or pyrrolidone derivatives having a K value of 10-120 and molecular weight ranging from 2500 to 3000000 are used.

42. A process as claimed in claims 35 to 41 wherein the amount of the film forming agent employed in making the active coating range from 20.0 mg to 200.0 mg and preferably 25.0 mg to 150.0 mg per gram of the composition.

43. A process as claimed in claims 35 to 42 wherein the excipients used in making the active coating are selected from materials such as microcrystalline cellulose powder, dicalcium phosphate, sodium lauryl sulphate, dioctyl sodium sulpho succinate, alginic acid, talc, titanium dioxide, starch and a mixture thereof.

44. A process as claimed in claims 35 to 43 wherein the amount of excipients employed in active coating ranges from 2.0 mg to 100.0 mg and preferably from 3.0 mg to 80.0 mg per gram of the composition.

45. A process as claimed in claims 35 to 44 wherein the coating solvents employed for active coating is purified water.

46. A process as claimed in claims 35 to 45 wherein the intermediate coating consists of a film forming agent and excipients.

47. A process as claimed in claims 35 to 46 wherein the film forming agent used in making the intermediate coating are selected from cellulose derivatives such as hydroxypropyl cellulose, hydroxypropyl methylcellulose, sodium carboxy methyl

cellulose, carboxy methyl cellulose and polyvinyl pyrrolidone derivatives / sodium alginate etc or a mixture therof.

48. A process as claimed in claims 35 to 47 wherein the cellulose derivatives in making the intermediate coating such as hydroxypropyl methylcellulose having a molecular weight of 10000 to 150000, hydroxypropyl cellulose having a molecular weight of 80000 – 1150000, hydroxyethyl cellulose having a varying viscosities 2-20000 mpa or pyrrolidone derivatives having a K value of 10-120 and molecular weight ranging from 2500 to 3000000 are used.

49. A process as claimed in claims 35 to 48 wherein the amount of the film forming agent employed in making the intermediate coating ranges from 20.0 mg to 200.0 mg, preferably 25.0 mg to 150.0 mg per gram of the composition.

50. A process as claimed in claims 35 to 49 wherein it contains excipients selected from materials such as microcrystalline cellulose powder, dicalcium phosphate, sodium lauryl sulphate, dioctyl sodium sulpho succinate, alginic acid, talc, titanium dioxide, starch and a mixture thereof.

51. A process as claimed in claims 35 to 50 wherein the amount of excipients used in making the intermediate coating ranges from 2.0.mg to 100.0 mg, preferably from 3.0 mg to 80.0 mg per gram of the composition.

52. A process as claimed in claims 35 to 51 wherein the coating solvents employed for intermediate coating is purified water.

53. A process as claimed in claims 35 to 52 wherein the polymer employed in the coating composition used for entering coating is selected from enteric polymers such as cellulose derivatives or methacrylic acid derivatives or the mixture thereof.

54. A process as claimed in claims 1 to 53 wherein the enteric coating polymeric composition also contains plasticizer and anti-adherents.

55. A process as claimed in claims 35 to 54 wherein the enteric coating polymeric composition also contains colorants and opacifiers.

56. A process as claimed in claims 35 to 55 wherein the cellulose derivatives such as Cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate and methacrylic acid derivatives such as Eudragit L 100 – 55, Eudragit L 30D-55 are used.

57. A process as claimed in claims 35 to 56 wherein the amount of enteric coating polymer used ranges from 20.0 mg to 300.0mg, preferably from 50.0 mg to 250.0 mg per gram of the composition.

58. A process as claimed in claims 35 to 57 wherein the plasticizer used is selected from materials such as fatty alcohol derivatives such as cetyl alcohol , stearyl alcohol or phthalate derivatives such as diethyl phthalate, dipropyl phthalate, dibutyl phthalate, dioctyl phthalate or polyethelene glycol derivatives having the molecular weight ranges of 200 to 10000 or a mixture thereof.

59. A process as claimed in claims 35 to 58 wherein the amount of plasticizer used ranges from 1.0 mg to 60.0mg and preferably from 2.0 mg to 50.0 mg per gram of the composition.

60. A process as claimed in claims 35 to 59 wherein the anti-adherents used is selected from materials such as talc, stearate, stearic acid, hydrogenated castor oil or the mixture thereof.

61. A process as claimed in claims 35 to 60 wherein the amount of anti-adherents used ranges from 2.0 to 120.0 mg, preferably from 4.0 mg to 100.0 mg per gram of the composition.

62. A process as claimed in claims 35 to 61 wherein the composition used in the enteric coating contains colorants and opacifiers selected from iron oxides, titanium dioxide, starch or mixture thereof.

63. A process as claimed in claim 62 wherein the amount of colorants and opacifiers used ranges from 0.1 mg to 40.0 mg, preferably from 0.5 mg to 30.0 mg per gram of the composition.

64. A process as claimed in claims 35 to 63 wherein the solvent used for enteric coating of the composition is selected from aqueous or organic solvents or mixture thereof.

65. A process as claimed in claims 35 to 64 wherein the aqueous solvent used is purified water and the organic solvents such as IPA, acetone, ethanol or mixture thereof is used.

66. A process as claimed in claims 35 to 65 wherein the pellets are filled into hard gelatin capsules of suitable size by conventional methods depending upon the drug assay and required therapeutic dose of the drug.

67. A process as claimed in claims 35 to 66 wherein sugar spheres are used as fillers or excipients to adjust the fill weight of the capsule.

68. A process for the preparation of an improved composition as claimed in claim 35 to 67 wherein the amount of sugar spheres used ranges from 1.0 mg to 150.0 mg, preferably 5.0 mg to 100.0mg per capsule based on the assay of enteric coated pellets and fill weight of capsules.

69. An improved and stable pharmaceutical composition in the form of hard gelatin capsule useful for treatment of gastric and duodenal ulcers substantially as herein described with reference to the Examples 1 to 12

70. A process for the preparation of an improved and stable pharmaceutical composition in the form of a hard gelatin capsule useful for treatment of gastric and duodenal ulcers substantially as herein described with reference to the Examples 1 to 12.